REMARKS

Reconsideration of the Office Action mailed April 12, 2004, (hereinafter "instant Office Action"), entry of the foregoing amendments and withdrawal of the rejection of claims 18-21 and 23-28 and 30-45, are respectfully requested.

Applicants observe that the Examiner has not mentioned the rejection of claim 18 under 35 U.S.C. §102(b), for allegedly being anticipated by Hiremath et al., and therefore, Applicants presume that the arguments and amendments submitted in the Preliminary Amendment filed concurrently with the Requested for Continued Prosecution filed on February 13, 2004 was persuasive and the rejections have been withdrawn.

In the instant Office Action, claims 18-21, 23-28 and 30-45 are listed as pending, and claims 18-21, 23-28 and 30-45 are listed as rejected. Claims 1-17 and 22 were previously cancelled by Applicants in the Reply filed May 15, 2002. The correct status of these claims is reflected in the listing of claims beginning on page 2 of this Reply. Claim 30 has been amended to make it depend from claim 28. Previously, claim 30 depended from claim 29 which has been cancelled. Claims 19-21, 40, 42 and 44 have been cancelled by the Applicants and this status is reflected in the listing of claims beginning on page 2 of this Reply. Applicants have amended claim 18 and support for this amendment can be found in the original Markush group, *inter alia*, at page 14, lines 10-13, of the instant application. Applicants have also amended claims 43 and 45 to reflect amended claim 18. Without conceding to the correctness of the Examiner's rejections and for the sole purpose of expediting prosecution of the instant application and to put it in condition for allowance, Applicants have amended claims 18, 43 and 45 without waiver or prejudice to Applicants' right to pursue the cancelled subject matter in a continuation or divisional application. Applicants have added new claims 46 and 47. Support for these claims can be found, *inter alia*, at page 12, line 10 to line 20.

The Examiner states "...[t]hat compounds, corresponding compositions, a method of use and a process of making that are of the same cope are considered to form a single inventive concept. Claims 18 and 28-39 are now of different scopes." The Examiner suggests that Applicants should either amend these claims so they are of the same scope or elect a group to be examined. Applicants respectfully point out that the claims do form a single inventive concept as they are. Claim 18 was rejected under 35 U.S.C. §102(b) over several references and was subsequently amended to overcome these rejections. Claims 28-39 did not receive these rejections and therefore were not amended. Claims 18 and 28-39 form a single inventive concept

in their current form in that no additional search is required on behalf of the Examiner. Any search done on these claims will result in the same references. As the Examiner has already done an extensive search and only found the references to be relevant to claim 18, the composition of matter claim. Thus, Applicants respectfully decline the Examiner's suggestion to either amend the claims or elect a group to be examined. Without conceding to the correctness of the Examiner's rejections and for the sole purpose of expediting prosecution of the instant application and to put it in condition for allowance, Applicants have cancelled claim 37 without waiver or prejudice to Applicants' right to pursue the cancelled subject matter in a continuation or divisional application.

The Examiner has rejected claim 18 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner alleges that the provisos that were inserted into claim 18 lack description. Applicants have amended claim 18 to remove the provisos. Based upon this amendment, the rejection of claim 18 under 35 U.S.C. §112, first paragraph, is obviated and should be withdrawn.

The Examiner states "Claim 28 is drawn to inhibiting one or more protein kinase activities selected from 16 kinases but one skilled in the art would not know how to use these compounds." Applicants respectfully traverse this rejection. The Examiner cites *In re Lorenz and Wegler*, 13 USPQ 312 U.S. Court of Customs and Patent Appeals. In *In re Lorenz and Wegler*, the court found that the only attempt to comply with the use requirements of Section 112 was found in the appellants specification which stated "A characteristic feature of the novel phosphoric acid ester is their low toxic effects against warm-blooded animals, while at the same time they have a good effect against a very wide range of insects." The court found that no one would know how to use one of the claimed compounds to kill even a single insect or whether the compounds were to be used as sprays, dusts or in another manner. With respect to the Examiner's comments that Applicants have not provided what is being treated by claim 28, Applicants respectfully direct the Examiner's attention to page 89, line 19 to page 90, line 19 of the instant specification wherein Applicants describe that the compounds of the invention have antiangiogenic properties due at least in part to the inhibition of protein tyrosine kinases and followed by a list the diseases in which the compounds can be used. With respect to the Examiner's comment that Applicants have not stated who the subject is in claim 28, claim 28 has been amended to add the phrase "to an

individual in need thereof". Support for this amendment can be found, *inter alia*, at page 92, lines 3-4. The Examiner asks how one can identify a subject in need. As stated above, Applicants have at page 89, line 19 to page 90, line 19 of the instant specification listed disease states the compounds of the instant invention can be used against. Therefore, any patient presenting with any of the aforementioned disease states would be "an individual in need". With respect to the Examiner's objection that Applicants have given no specific dose, given no specific dosing regimen and given no specific route of administration, Applicant respectfully direct the Examiner's attention to the Pharmaceutical Formulation section on pages 95-104 of the instant specification wherein Applicants describe routes of administration. Applicants particularly direct the Examiner's attention to page 102, lines 15-17 of the instant application wherein it states "The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician." Only the physician directing the care of a patient can determine the best course of treatment (route of administration, dosage) for a patient depending upon factors specific to each individual patient (weight, severity of disease). Claims are to be read in light of the specification. The specification clearly conveys to one skilled in the art what is being treated by claim 28, who the subject is, how one can identify said subject, and how dosage, dosing regimen and route of administration can be determined.

Second, from this language it appears that the Examiner may be applying approval by the Food and Drug Administration as the standard for utility and/or enablement under the patent statues. Applicants direct the Examiner's attention to M.P.E.P. 2107.02 V. which states:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. *In re Brana* 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995) (citing *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994)).

The foregoing passage clearly indicates that it is not necessary that a compound obtain approval from or be approvable by the Food and Drug Administration in order to meet the enablement requirement of 35 U.S.C. §112, first paragraph. The statute only requires an applicant to show how to make and how to use an invention. In the instant application, Applicants have shown how to make and use a compound of formula I or a pharmaceutically acceptable salt thereof for inhibiting one or more protein kinase activities.

Third, the Examiner's allegation strongly suggests that the Examiner has confused the requirement for utility versus the requirement for enabling how to make and how to use. The Examiner's rejection seeks proof that a compound of formula I is effective in inhibiting one or more protein kinase activities. However, such evidence is not required for patentability. Applicants direct the Examiner's attention to M.P.E.P. 2107.02 V, which states:

> Thus, while an applicant may on occasion need to provide evidence to show that an invention will work as claimed, it is improper for Office personnel to request evidence of safety in the treatment of humans, or regarding the degree of effectiveness. See *In re Sichert*, 566 F.2d 1154, 196 USPQ 209 (CCPA 1977); *In re Hartop*, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); *In re Anthony*, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969); *In re Watson*, 517 F.2d 465, 186 USPQ 11 (CCPA 1975); *In re Krimmel*, 292 F.2d 948, 130 USPQ 215 (CCPA 1961); *Ex parte Jovanovics*, 211 USPQ 907 (Bd. Pat. App. & Inter. 1981).

Applicants respectfully submit that the inquiry that has to be answered to meet the enablement requirement is best phrased as follows: "if one were to use a compound of formula I inhibiting one or more protein kinase activities, how would one do it?". This is a very different question from the question that the Examiner is asking, which is best phrased as follows: "if one were to use a compound of formula I inhibiting one or more protein kinase activities, would it work?". Applicants respectfully submit that it is the first phrased question that has to be satisfied to meet the enablement requirement of 35 U.S.C. §112, first paragraph. Applicants submit that Applicants have answered the question by detailing: (1) how one of ordinary skill in the art would obtain a compound of formula I; (2) how one of ordinary skill in the art would formulate a compound of formula I; and (3) how one of ordinary skill in the art would administer such a formulation of a compound of formula I to inhibit one or more protein kinase activities.

If the Examiner's question was what had to be answered to satisfy 35 U.S.C. §112, first paragraph, then all pharmaceutical patent applications would have to include clinical efficacy data. This is not the case. In fact, the M.P.E.P. cautions against requiring such data. Applicants direct the Examiner's attention to M.P.E.P. 2107.02 IV, which states:

> Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders (see *In re Isaacs*, 347 F.2d 89, 146 USPQ 193 (CCPA 1963); *In re Langer*, 503 F.2d 1380, 183 USPQ 288 (CCPA 1974)), even with respect to

situations where no art-recognized animal models existed for the human disease encompassed by the claims.

The Examiner cites *In re Moureu and Chovin*, 145 USPQ 452, in which the U.S. Court of customs and Patent Appeals found that the application contained no disclosure of the utility and methods of using the claimed compounds other than statements that the compounds were found to possess highly useful pharmacological properties, substantial anti-tubercular activity and could be employed in veterinary medicine against five different conditions. The court also found that the appellants had not disclosed or suggested the manner of administration. The instant case differs in that Applicants have described routes of administration and stated that exact dosage and administration must be determined by the treating physician. Further, Applicants have provided assays which can be used to test the efficacy of the compounds with regard to kinase inhibition, not merely stated that the compounds of the instant invention are useful as kinase inhibitors. With respect to the court's finding that "...those skilled in the art who desire to use the products of the invention for medicinal purposes would find it necessary to engage in extensive experimentation to determine what would be the effective and safe manner of using the products as medicines for the suggested purposes and to determine the dosages to be avoided because lethal of ineffective", Applicants submit that safety is the province of the U.S. Food and Drug Administration, not the U.S. Patent and Trademark Office.

With respect to the Examiner's citation of *Brenner v. Manson*, 148 USPQ at 696, and the finding that "...it was not the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statues by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless...", Applicants respectfully point out that in the instant application Applicants have taught how to make and use the compounds of the invention as well as provided assays which can be used to test the effectiveness of each compound as a kinase inhibitor. Applicants have taught how to use the compounds of the instant invention in the Pharmaceutical Formulation section of the application on pages page 95, line 18 through page 105, line 5. Applicants have taught that there are diseases which can be affected by inhibition of certain kinases page 89, line 19 to page 90, line 19 and written claims drawn to using the instant compounds to treat said diseases. Applicants have provided a detailed explanation of how, using

the compounds of the instant invention, the inhibition of protein kinase activity can be used in a therapeutic context

With respect to whether one would find it necessary to engage in extensive experimentation to determine what would be the effective and safe manner of using the products as medicines, the amount of experimentation need to determine the effective and safe manner of using the products as medicines is routine in the pharmaceutical industry. Thus the experimentation required would not be considered extensive.

Therefore, Applicants have met the statutory requirements of 35 U.S.C. §112, first paragraph. Accordingly the rejection of claim 18 under 35 U.S.C. §112, first paragraph, is obviated and should be withdrawn.

The Examiner has rejected claims 37 and 38 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection. The Examiner states that the basis of this rejection is the same as given in the previous office action. However, the Examiner did not previously reject claims 37 and 38 under 35 U.S.C. §112, first paragraph. The Examiner also mentions a method of treating neurodegenerative disorders. Applicants respectfully point out that neither claim 37 nor claim 38 mentions neurodegenerative disorders. The Examiner alleges that the origin and the nature of the diseases listed in claims 37 and 38 are different from one another and that alleging that "[t]he ability to treat any and all of the diseases recited in these claims is prima facie not enabled." However, the diseases listed in claims 37 and 38 share a common thread. Each has an angiogenic component. On page 89, line 19 to page 90, line 19 of the instant specification Applicants describe that the compounds of the invention have antiangiogenic properties due at least in part to the inhibition of protein tyrosine kinases. Compounds with antiangiogenic properties due to inhibition of kinases can logically be used to treat diseases that have an angiogenic component.

Based upon the foregoing, the rejection of claims 37 and 38 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, is obviated and should be withdrawn.

The Examiner has rejected claims 18-21, 23-28 and 30-45 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject

matter which applicant regards as the invention. Applicants respectfully traverse this rejection. The Examiner states that the phrase "lower alkyl ester" in the definitions of R^3, R^4 and R^5 is not a radical but a compound. Applicants respectfully point out that it is in the definition of suitable substituents for R^3, R^4 and R^5 that the term "lower alkyl ester" appears, not in the definitions of R^3, R^4 and R^5 themselves. One of ordinary skill in the art would understand that an ester is a compound in which the –OH of a carboxyl group has been replaced by –OR and that the ester would attach to R^3, R^4 or R^5 in the same manner as cycloalkyl or lower alkyl, which are also listed as suitable substituents for R^3, R^4 and R^5. Based upon the foregoing, the rejection of claims 18-21, 23-28 and 30-45 under 35 U.S.C. §112, second paragraph, is obviated and should be withdrawn.

The Examiner has rejected claim 18 under 35 U.S.C. §102(b) as being anticipated by Barnikow et al. (Chemische Berichte (1967), 100(5), 1661-6. The Examiner alleges that Barnikow et al. teaches the compound with RN 16105-53-6 which corresponds to the compound of the instant claim when in the instant case R^1 is –OiPr and R is nitrophenyl. Applicants have amended claim 18 and it no longer reads upon the compound with RN 16105-53-6 where R^1 is –OiPr and R is nitrophenyl. Thus, the rejection of claim 18 under 35 U.S.C. §102(b) as being anticipated by Barnikow et al. is obviated and should be withdrawn.

The Examiner has rejected claim 18 under 35 U.S.C. §102(b) as being anticipated by Misawa et al. (JP 52051366). The Examiner alleges that Misawa et al. teaches the compound with RN 63554-75-6 which corresponds to the compound of the instant claim when in the instant case R^1 and R are both phenyl groups. Applicants have amended claim 18 and it no longer reads upon the compound with RN 63554-75-6. Thus, the rejection of claim 18 under 35 U.S.C. §102(b) as being anticipated by Misawa et al. is obviated and should be withdrawn.

The Examiner has rejected claim 18 under 35 U.S.C. §102(b) as being anticipated by Ege et al. (Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999) (1983), (2), 325-31). The Examiner alleges that Ege at al. teaches the compound with RN 85921-36-4 which corresponds to the compound of the instant claim when in the instant case R^1 is hydrogen and R is methoxyphenyl. Applicants have amended claim 18 and it no longer reads upon the compound with RN 85921-36-4 where R^1 is hydrogen and R is methoxyphenyl. Thus, the rejection of claim 18 under 35 U.S.C. §102(b) as being anticipated by Ege et al. is obviated and should be withdrawn.

The Examiner has rejected claim 18 under 35 U.S.C. §102(b) as being anticipated by Schmidt et al. (Journal of Organic Chemistry (1983), 48(23), 4367-70). The Examiner alleges that Schmidt et al. teaches the compounds of RN 87192-00-5, 87192-01-6, 87192-02-7, 87192-03-8 and 87192-04-961-14-6 which corresponds to the compound of the instant claim when in the instant case R^1 is hydroxymethyl and R represents trimethoxyphenyl, chlorophenyl, phenyl and nitrophenyl. Applicants have amended claim 18 and it no longer reads upon the compounds with RN 87192-00-5, 87192-01-6, 87192-02-7, 87192-03-8 and 87192-04-961-14-6. Thus, the rejection of claim 18 under 35 U.S.C. §102(b) as being anticipated by Schmidt et al. is obviated and should be withdrawn.

The Examiner has rejected claim 18 under 35 U.S.C. §102(b) as being anticipated by Imai et al. (JP 6202570). The Examiner alleges that Imai et al. teaches the compound with RN 108402-26-2 which corresponds to the compound of the instant claim when in the instant case R^1 is methyl and R is 4-hydroxy-3,5-bisiopropyl phenyl. Applicants have amended claim 18 and it no longer reads upon the compound with RN 108402-26-2. Thus, the rejection of claim 18 under 35 U.S.C. §102(b) as being anticipated by Imai et al. is obviated and should be withdrawn.

The Examiner has rejected claim 18 under 35 U.S.C. §102(b) as being anticipated by Dubau et al. (Chemische Berichte (1983), 116(7), 2714-16). The Examiner alleges that Dubau et al. teaches the compound with RN 87161-14-6 which corresponds to the compound of the instant claim when in the instant case R^1 is hydroxy and R is dimethylamino phenyl. Applicants have amended claim 18 and it no longer reads upon the compound with RN 87161-1416. Thus, the rejection of claim 18 under 35 U.S.C. §102(b) as being anticipated by Dubau et al. is obviated and should be withdrawn.

The examiner has rejected claim 18 under 35 U.S.C. §102(b) as being anticipated by Mitra et al. (Acta Ciencia Indica, Chemistry (1985), 11(4), 267-72. The Examiner alleges that the reference teaches the compounds which correspond to the compound of the instant claim when in the instant case R^1 is hydrogen and R is phenyl, hydroxyphenyl, nitrophenyl, methoxyphenyl and 3-bromo-2-hydroxyhenyl. Applicants have amended claim 18 and it no longer reads upon these compounds. Thus, the rejection of claim 18 under 35 U.S.C. §102(b) as being anticipated by Mitra et al. is obviated and should be withdrawn.

The Examiner has again rejected claim 18 under 35 U.S.C. §103(a) as being unpatentable over Blum et al. (US 6,107,487). The reference teaches the compound of example 10 and the Examiner alleges that the claim differs by having a hydrogen over the prior art methyl on the ring

nitrogen of the pyrazolinone. Based upon Applicants' amendment of claim 18 the rejection of claim 18 under 35 U.S.C. §103(a) as being unpatentable over Blum et al. (US 6,107,487) is obviated and should be withdrawn.

The Examiner has rejected claim 18 under 35 U.S.C. §102(b) as being anticipated by Fathy et al. (Journal of Chemical and Engineering Data (1988), 33(2), 218-19). The Examiner alleges that the reference teaches the compound with RN 113111-06-1 which correspond to the compound of the instant claim when in the instant case R^1 is amino and R is 2-chloro-7-methyl-3-quinolinyl. Applicants have amended claim 18 and it no longer reads upon the compound with RN 113111-06-1.

Based upon the foregoing, Applicants believe that claims 18-21 and 23-39 and 41-45 are in condition for allowance. Prompt and favorable action is earnestly solicited.

If the Examiner believes that a telephone conference would advance the condition of the instant application for allowance, Applicants invite the Examiner to call Applicants' agent at the number noted below.

Respectfully submitted,

Date: September 13, 2004

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